Sequential High-Dose Methotrexate and Fluorouracil Combined With Doxorubicin—A Step Ahead in the Treatment of Advanced Gastric Cancer: A Trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group

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In a prospective phase III multicenter trial, 213 patients with advanced measurable or nonmeasurable gastric cancer were randomized to receive methotrexate (MTX), fluorouracil (5-FU), and Adriamycin (doxorubicin; Farmitalia Carlo Erba, Milan, Italy) (FAMTX) or 5-FU, Adriamycin, and mitomycin (FAM). The results show a significantly superior response rate (41% v 9% [$P < .0001$]), and survival (median, 42 weeks v 29 weeks [$P = .004$]) for FAMTX. There was a cumulative thrombocytopenia in FAM and not in FAMTX. The FAMTX protocol should be the reference treatment in future clinical trials that seek to improve the therapeutic outcome in advanced gastric cancer.

J Clin Oncol 9:827-831. © *1991 by American Society of Clinical Oncology.*

IN 1982, KLEIN ET AL[1] reported a 63% response rate in patients with advanced gastric carcinoma treated with sequentially high-dose methotrexate (MTX) and fluorouracil (5-FU), combined with Adriamycin (doxorubicin; Farmitalia Carlo Erba, Milan, Italy) (FAMTX). In an update of this study, 59 responders of 100 patients were reported, including 12 complete responses and a median survival of all patients of 9 months. There were three toxic deaths.[2]

The European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal (GI) Tract Cooperative Group has conducted a multicenter phase II trial evaluating this protocol. The response rate was 33% including some histologically documented complete responses, but the toxicity was of concern.[3] Therefore, it was decided to further assess FAMTX in a randomized phase II design comparing it with 5-FU, Adriamycin, and mitomycin (FAM), which still was considered by the majority of investigators to be the standard treatment for advanced gastric cancer.

The primary aim of this study was to evaluate more precisely the toxicity of FAMTX. An interim analysis performed after randomization of 50 patients demonstrated that there were no major differences in the toxicity of both schedules,[4] and therefore, the study was extended to a phase III with the purpose of comparing response rate and survival. A total of 200 patients was anticipated in order to confirm or reject a 50% gain in the median survival, assuming a maximum of 10% losses due to noneligibility or nonassessability. The results are presented in this report.

PATIENTS AND METHODS

MTX was given in a dose of 1,500 mg/m^2 intravenously (IV) followed after 1 hour by 5-FU 1,500 mg/m^2 IV day 1; leucovorin rescue was started after 24 hours, 15 mg/m^2, orally every 6 hours for 48 hours; and Adriamycin 30 mg/m^2, IV was administered on day 15. Optimal hydration (diuresis $\geq$ 100 mL/h), alkalinization of the urine before administering MTX, and monitoring of the plasma MTX level were mandatory. In cases of elevated values of the MTX level, adjustment of the leucovorin dose had to be made. Cycles were repeated every 4 weeks. The FAM regimen consisted of 5-FU 600 mg/m^2 IV days 1, 8, 29, and 36; Adriamycin 30 mg/m^2 IV days 1 and 29; and mitomycin 10 mg/m^2 IV day 1. Cycles had to be repeated every 8 weeks. Chemotherapy had to be postponed for a maximum of 2 weeks in case of a WBC count of less than 3.0×10^9/L or platelets of less than 70×10^9/L on the day of treatment. If after a maximum delay of 2 weeks the WBC count was between 2 and 2.9 and/or platelets between 50 and 69×10^9/L, a 50% dose

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Submitted August 8, 1990; accepted November 1, 1990.

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0732-183X/91/0905-0011$3.00/0

reduction had to be made in the FAMTX arm, while mitomycin had to be omitted in the FAM arm. In case of lower values, patients had to be taken off study. In cases of nadir values for a WBC count of less than 1.0×10^9/L, a 25% dose reduction of 5-FU/MTX had to be given in the FAMTX arm and mitomycin had to be omitted in the FAM arm.

Eligibility criteria included age 75 years or younger, histologically documented advanced gastric cancer, no previous chemotherapy (except in adjuvant setting) or radiotherapy, and adequate organ functions. Stratification was made for measurable or assessable versus nonmeasurable disease and for institution. Computed tomographic (CT) scans and ultrasound were strongly recommended for measurement of the disease, although palpation of clearly measurable lesions was still accepted. Measurable lesions were lesions that could be clearly demarcated in two dimensions preferably by CT scan or ultrasound. Assessable lesions were lesions that could be evaluated for response by CT scan or ultrasound, but which could only be clearly measured in one diameter, ie, diffuse liver metastases, not clearly bidimensionally demarcated abdominal masses, etc.

Definition of response was according to World Health Organization (WHO) criteria. Briefly, a complete response required complete disappearance of all clinical evidence of disease. Partial remission required a more than 50% reduction in the sum of the products of the two largest perpendicular diameters of bidimensionally measurable lesions or a more than 30% reduction in the sum of the diameters of assessable lesions. All responses had to be extramurally reviewed before being accepted.

Differences in the response rate were compared by means of a Fisher's exact test. Survival was measured from the start of therapy using the method of Kaplan and Meier. Differences in the survival were compared using a log-rank test with adjustment for covariates. Toxicity was graded according to the WHO criteria.

RESULTS

Until September 7, 1989, 213 patients (108 FAMTX, 105 FAM) from 31 institutions were randomized. Five patients were not eligible, three in the FAMTX arm and two in the FAM arm because of nonconformity to histology (two), laboratory data, or performance status (three), and from two other patients, no follow-up data were received. Five patients were considered nonassessable because they refused treatment after randomization or were lost to follow-up after the first day of chemotherapy. However, these patients were kept in the survival curves. A total of 41 patients had nonmeasurable lesions and were only assessable for toxicity and survival. In 81 patients in FAMTX and in 79 patients in FAM with measurable (71 and 70, respectively) or assessable (10 and 9, respectively) lesions, response could be assessed. Patient characteristics in both arms of the study were well balanced for possible prognostic factors and are depicted in Table 1.

Toxicity

The median number of cycles in FAM was one (range, one half to six; one cycle, 8 weeks) and in FAMTX four (range, one to 16; one cycle, 4 weeks). There were no major differences in the nonhematologic toxicity, but mucositis was more pronounced in FAMTX (Table 2). There were no differences in leukocyte nadirs, but there was a cumulative thrombocytopenia in the FAM arm (Tables 3 and 4). Dose reduction or postponement of treatment occurred in 21% of the patients in FAMTX and in 15% of the patients in FAM. Overall, more than 85% of the intended dose intensity was actually reached in both treatment arms. There was one toxic death due to granulocytopenic sepsis in FAMTX and two in FAM, while in two other patients treated with FAMTX, it could not be excluded that toxicity contributed to their death. One of these patients died at home 1 week after the first cycle, possibly from a perforation. This patient received several drugs that

Table 1. Patient Characteristics of Eligible Patients

Characteristic	FAMTX (n = 105)	FAM (n = 103)
Age (years)		
Median	57	58
Range	28-77	23-69
Sex		
M/F ratio	76/29	77/26
Performance status		
WHO 0	29	29
WHO 1	52	50
WHO 2	23	21
Unknown	1	3
Weight loss		
None	25	25
≤ 10%	39	33
> 10%	40	44
Unknown	1	1
Extent of disease		
Locoregional	19	13
Primary excised, metastatic	35	32
Primary not excised, metastatic	38	50
Locoregionally recurrent and metastatic	11	6
Unknown	2	2
Prior surgery		
None	32	39
Curative	23	26
Palliative	49	38
Unknown	1	
Prior adjuvant chemotherapy	3	1

Table 2. Nonhematologic Toxicity

	FAMTX %	FAM %
Nausea/vomiting	63	74
WHO grade 3	8	8
Mucositis	51	20
WHO grade 3	10	1
Diarrhea	26	17
Alopecia		
WHO grade 3	24	20

should have been withheld during chemotherapy, and the patient had a clearly elevated MTX level after the first cycle. He received no adequate leucovorin rescue according to the elevated MTX level and was dismissed from the hospital prematurely. The other patient experienced grade 4 hematologic toxicity and fever but refused to come to the hospital for supportive care and died shortly later at home. A third patient treated with FAM died of the hemolytic uremic syndrome. These data show that the toxicity experienced by the patients treated with FAMTX was acceptable and comparable with that of the patients treated with FAM.

Response

There were a total of 160 patients who were fully assessable for response. There were 33 responses in FAMTX and seven in FAM ($P < .0001$) (Table 5). In three patients, two in FAMTX and one in FAM, the response was documented by caliper only, and in one other patient in the FAMTX arm, by negative endoscopy. Response was assessed by ultrasound in two patients treated with FAM and in eight patients treated with FAMTX. All other responses were documented by CT scan. In seven of 19 patients with locally advanced disease in FAMTX, a second-look operation was performed with the aim of removing residual tumor, which was achieved in three of them. In the other four patients, there was a more than 50% reduction of tumor mass, but the lesions were still unresectable.

Table 3. Leucocyte Toxicity in Successive Courses

	FAMTX		FAM*	
Course No.	Nadir	Range	Nadir	Range
1	3.1	0.5-12.0	4.0	0.1-26.3
2	3.6	0.7-12.4	4.0	1.0-9.4
3	3.2	1.0-9.7	3.5	0.8-7.2
4	3.7	0.7-10.7	3.4	0.8-5.5
5	3.0	1.4-9.4	2.3	0.7-4.4
6	3.3	1.9-6.0	3.4	1.6-3.9

*One course in FAM is presented as a 4-week period.

Table 4. Thrombocyte Toxicity in Successive Courses

	FAMTX		FAM*	
Course No.	Nadir	Range	Nadir	Range
1	205	9-574	173	20-429
2	214	48-538	141	17-380
3	193	45-486	120	8-248
4	185	27-462	70	27-215
5	180	66-375	104	28-175
6	200	114-354	27	26-86

*One course in FAM is presented as a 4-week period.

Survival

All eligible patients with available follow-up were included in the survival analysis. The follow-up is quite complete as 148 patients (72%) have died. The median survival for the patients treated with FAMTX was 42 weeks versus 29 weeks for patients treated with FAM (log-rank test, $P = .004$) (Fig 1). The 1-year survival in FAMTX was 41% versus 22% in FAM. The 2-year survival rates were, respectively, 9% and 0%.

DISCUSSION

The results of this EORTC study demonstrate that the FAMTX regimen yields a superior response rate and survival as opposed to FAM, with less hematologic toxicity.

The response to FAM in this study is lower than generally reported. This is probably due to differences in the methods used to assess the response. Although palpation was still accepted for the assessment of response in the present study, the vast majority of responses were documented by CT

Table 5. Response Comparisons

	FAMTX (n = 81)	FAM (n = 79)
Complete response	5	0
Partial response	28	7
No change	25	25
Progression	16	34
Early deaths	7	13
Response rate	41%	9%
Details on early deaths		
Malignant	2	10
Toxic	1	2
Other	4	1

NOTE. Response FAMTX versus FAM (Fisher's exact test) $P < .0001$.

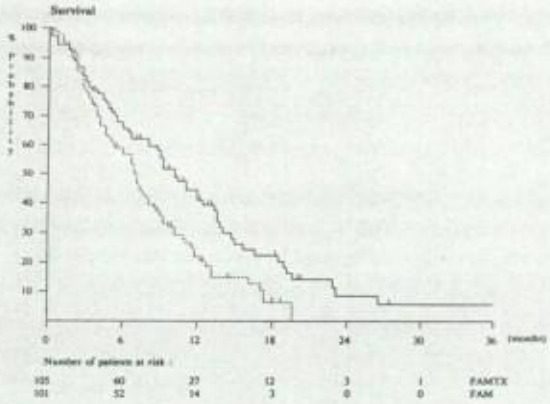

Fig 1. Survival curves for separate arms of the study. Stomach (40851): (—) FAMTX, no. of patients 105, died 69; (-----) FAM, no. of patients 101, died 79 (log-rank $P = .004$).

scans, and all documents were extramurally reviewed. Clinical measurements by caliper can be biased by the investigator's interpretation and can not be reviewed.

No other randomized study, with FAM as one of the treatment arms, has been reported in which superior results with other combinations or with 5-FU alone were achieved as opposed to FAM. Similar results as ours obtained with FAMTX in this study have been reported in phase II studies by other groups using different chemotherapy regimens, especially the combination of etoposide, Adriamycin, and cisplatin (EAP), which has gained interest since the excellent treatment results reported from Germany.[5] The precise impact of EAP, however, should be demonstrated in a randomized study. The response and toxicity of FAMTX as reported in this study is corroborated by the preliminary results of an ongoing randomized study conducted in Memorial Sloan-Kettering Cancer Center comparing FAMTX with EAP. In 39 patients, the response to FAMTX was 31% versus 24% to EAP and the toxicity of FAMTX was less.[6]

The overall response rate in both arms of our study was not essentially changed by the process of extramural review. However, three complete responses in FAMTX were considered partial responses and grouped as such, because minimal residual lesions could not be excluded by the reviewer. Two partial responses in FAM were considered minor responses and therefore grouped as stable disease.

There are a few other randomized trials in advanced gastric cancer, conducted by the Gastrointestinal Tumor Study Group (GITSG), which yielded a significant survival difference between separate arms of the study. In the study most recently reported by the GITSG, 5-FU, Adriamycin, and cisplatin (FAP) and 5-FU, Adriamycin, and triazinate (FAT) were compared with 5-FU, Adriamycin, and lomustine (MeFA), which was the best regimen in their older studies. FAP and FAT resulted in a significantly superior survival, but there were no differences in the response rate between the three regimens, and the median survival was 31 and 30 weeks versus 23.5 weeks.[7] A comparison of the survival between this and other randomized studies and our trial, however, is potentially flawed by differences in the inclusion of patients with only locally advanced disease and by the definition and inclusion of patients with nonmeasurable disease.

Although all drugs combined in FAMTX have activity in gastric cancer, the main rationale for this regimen is based on the enhanced cytotoxicity of 5-FU provoked by pretreatment with MTX, which is presumed to act as a modulating agent. The optimal dose and timing of MTX, however, is unknown and the clinical applicability of the synergy concept, which has a sound biochemical basis,[8,9] remains investigational.[10] Attempts to modify the MTX/5-FU schedule as used in FAMTX, mainly by reducing the dose of MTX, so far have been unrewarding. In four trials, the dose of MTX ranged from 100 to 600 mg/m^2 and the response rate from 0% to 21%.[11] Although a formal comparison between high-dosage and low- or intermediate-dosage MTX has not been undertaken in gastric cancer, in view of available clinical data, such a trial does not appear particularly warranted.

The possibility that leucovorin, which is administered as a rescue for high-dose MTX, enhances the activity of 5-FU seems remote considering the 23-hour interval between the two drugs. We feel that MTX/5-FU as used in FAMTX should remain unchanged in future variants of the regimen that seek to improve the results.

FAMTX has demonstrated superiority over FAM and is a step ahead in the treatment of advanced gastric cancer. However, it is obvious that the therapeutic results are still modest. Fur-

thermore, the method of MTX administration is expensive and demanding. Therefore we do not advocate this regimen as "standard" treatment in advanced disease outside clinical trials. Nevertheless, we recommend that FAMTX be the reference arm in future randomized studies that seek to improve the therapeutic outcome in patients with advanced gastric cancer.

APPENDIX

The following investigators contributed at least three assessable patients to this study: H. Bron, Maasland Ziekenhuis, Sittard, The Netherlands; F. Cavalli, Ospedale San Giovanni, Bellinzona, Switzerland; E. Diaz-Rubio, Hospital San Carlos, Madrid, Spain; H. Hillen, Catharina Ziekenhuis, Eindhoven, The Netherlands; U. Kleeberg, Häemat. Onk. Poliklinik Ancona, Hamburg, Germany; J. Neijt, Academisch Ziekenhuis, Utrecht, The Netherlands; R. Obrist, Kantonsspital, Basel, Switzerland; B. Paillot, Centre Henri Bequerel, Rouen, France; and C. Veenhof, Academisch Medisch Centrum, Amsterdam, The Netherlands.

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